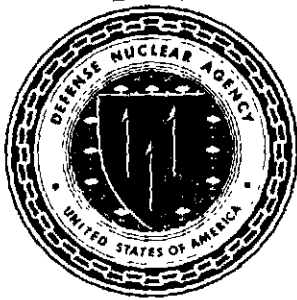


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RADIATION EFFECTS IN MAN: MANIFESTATIONS AND THERAPEUTIC EFFORTS

HEADQUARTERS
Defense Nuclear Agency
Washington, D.C. 20305



PREPARING AGENCY
University of Cincinnati College of Medicine
Cincinnati General Hospital
Cincinnati, Ohio 45229

Contract No. DASA-01-69-C-0131

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**Eugene L. Saenger, M.D. • Edward B. Silberstein, M.D.
Bernard S. Aron, M.D. • Harry Horwitz, M.D.
James G. Kereiakes, Ph. D. • I-Wen Chen, Ph. D.
Carolyn Winget, M.A. • Goldine C. Gleser, Ph. D.**

REPORT PERIOD
1 April 1971 through 31 March 1972

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INTRODUCTION

During the present contract period 1 April 1971 through 31 March 1972, we analyzed in great detail the results of whole- and partial-body radiation in the cancer patients treated between 19 February 1960 and 31 August 1971. Section 1 of this report comprises the scientific communication presented at the meeting of the American Roentgen Ray Society in Washington on 3 October 1972. This report has been accepted for publication in the American Journal of Roentgenology, Radium Therapy and Nuclear Medicine.

Section 2 of this report presents a study of the use of thermography to estimate radiation dose to skin in patients receiving ^{60}Co therapy. This method was not successful in identifying skin erythema or increased skin temperature even if such effects were present.

FOREWORD

This report was prepared by the following members of the University of Cincinnati College of Medicine:

Eugene L. Saenger, M.D.
Edward B. Silberstein, M.D.
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Carolyn Winget, M.A.
Goldine C. Gleser, Ph. D.

The research was supported by the Medical Directorate, Defense Nuclear Agency, Washington, D.C. under Contract No. DASA-01-69-C-0131. The Project Officer for the contract was Lt Col J. W. Cable.

These studies were performed in conformation with the "recommendations guiding doctors in clinical research" as stated in the Declaration of Helsinki of the World Medical Association (1964) and have been approved by the Committee on Human Research of the University of Cincinnati College of Medicine.

Research was conducted according to the principles enunciated in the "Guide for Laboratory Animal Facilities and Care," prepared by the National Academy of Sciences, National Research Council.

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SECTION 1

WHOLE-BODY AND PARTIAL-BODY RADIOTHERAPY OF ADVANCED CANCER

Introduction

The purpose of these investigations has been to improve the treatment and general clinical management and if possible the length of survival of patients with advanced cancer. Systemic effects of radiation therapy have been given particular attention in our work.

In the period 19 February 1960 through 31 August 1971, 85 adults were given whole- or partial-body radiation as therapy for far advanced cancer. This paper will report on the survival of patients in three categories: colon, lung, and breast. Prophylactic whole-body radiation therapy was given to three children with localized Ewing's sarcoma, and this experience will be discussed briefly. Investigations of biochemical, cytological, and psychological tests have been reported elsewhere (references 8, 11, and 50). Our experience with the adjunct use of autologous bone marrow will also be described.

Animal Studies

The animal investigations basic to our work stem from the studies of Hollcroft *et al* (references 13, 14, and 15). These authors demonstrated better tumor regression when whole-body radiation was preceded by localized radiation therapy than when localized radiation was given alone both for lymphoma and carcinoma in mice. The studies of Jacobson *et al* (references 18 and 19) showed the importance of shielding of the spleen and other organs and parts of the body in preventing high dose radiation lethality in the mouse.

Brief Review of Total-Body Radiation in Man

Total-body irradiation was first employed in 1923 by Chaoul and Lange (reference 7). Its use in 270 cases over the next 20 years was reviewed by Medinger and Craver (reference 32). These authors found the greatest palliation in the lymphomas and myeloproliferative diseases but also noted improvement in multiple myeloma. Thirty-five patients with advanced carcinoma or sarcoma

were included in this series, most of them receiving their total-body radiation between 1931 and 1933.

Loeffler *et al* (reference 30) compared total-body radiation in single doses up to 150 R with nitrogen mustard and triethylene melamine and found that neither chemotherapy nor radiotherapy differed in hematologic effects but that the patients receiving radiation did not experience the malaise of varying severity noted by all patients receiving the chemotherapeutic agents. Subjective improvement was noted only in the radiotherapy group.

Collins and Loeffler (reference 9) gave total-body irradiation in single exposure up to 200 roentgens and found this form of systemic therapy "a useful addition to the management of advanced cancer." The malignancies treated included lymphoma, chronic myelogenous leukemia, and multiple myeloma.

Interest in total-body radiation in the treatment of Ewing's sarcoma, a tumor of children which carries a high mortality, has been aroused by reports from Milburn *et al.* (reference 33) Jenkin *et al.* (reference 21) and Rider and Hasselback (reference 39). In a small series so treated, survival appeared to be moderately improved compared to larger series treated by conventional local radiotherapy and/or ablative surgery. These groups felt further evaluation of this form of therapy to be most important.

Additional data have been published by the Medical Division of Oak Ridge Associated Universities (reference 1), concerning total-body radiation therapy of lymphoproliferative, and myeloproliferative disease.

Summaries of the frequent use of total-body irradiation for the therapy of leukemia appear in an article by Buckner *et al.* (reference 4) and in a comprehensive review of bone marrow transplantation by Bortin (reference 3).

Whole-body radiation in routine clinical therapy has been and is currently used for leukemia (references 23 and 53), lymphoma (references 22 through 26, and 53), Hodgkin's disease (reference 3), polycythemia vera (reference 6), cancer of breast (reference 31), cancer of thyroid (reference 5), cancer of prostate (references 10 and 31), and multiple myeloma (references 9 and 32). Such therapy may be given by external radiation therapy (as in this particular study) or in the form of various radionuclides.

Study Design

The studies reported here were initially considered as being in Phase I (to determine whether the treatment was toxic or not) and subsequently as Phase II (whether treatment appears effective or not but without controls). In reviewing these data it has been possible to find some comparable material in the literature. In one category, cancer of bronchus, comparable data were available in our institution.

Informed Consent and Institutional Review

All patients gave informed consent in accordance with directives of the Faculty Research Committee of the University of Cincinnati College of Medicine and those of the National Institutes of Health. The use of formal informed consent forms in this study antedated the above requirements by 2 years. The project is reviewed and approved regularly by the above Committee.

Eligibility of Patients

Patients become eligible for this form of treatment if they have advanced cancer for whom cure could not be anticipated. Three children with localized Ewing's tumor at Children's Hospital were given whole-body radiation as part of the curative attempt after the primary tumor had been ablated with local radiotherapy.

Biopsy proof of the malignancy has been established in all instances. Clinical data in each case have been reviewed by several physicians to be certain that the tumor had indeed extended from its primary site and that curative therapy was not applicable. This preliminary evaluation is followed by an observation period of 7 to 14 days to observe the general condition of the patient and to carry out baseline laboratory tests to be as certain as possible that the condition of the patient is relatively stable. Frequently this determination is difficult since the patients have serious illnesses of long standing and often have had considerable previous therapy.

Patients remain in the hospital as long as is necessary. Prior to the use of autologous bone marrow transfusion, hospitalization was occasionally as long as 8 to 10 weeks. Length of stay was also dependent upon the severity of the clinical manifestations stemming from the cancer. With the use of partial-body

radiation and bone marrow infusion, hospitalization has been greatly shortened. The follow-up procedure is continuous during the lifetime of the patient.

A total of 112 subjects were initially entered in the study through 31 August 1971. During the screening period of 7 to 14 days, 24 of them (21 percent) were not continued in the study and did not receive whole- or partial-body radiation. Chief among the reasons for elimination was an indication in the pretreatment phase that some risk from wide-field radiation might ensue or that another method of treatment was considered preferable. In some, a very rapid progress of the disease made inclusion undesirable. The treatment was completed in 85 adults and three children between April 1960 and 31 August 1971. Three patients have received two separate courses of treatment in this program. Follow-up time for survivors is reported through 31 August 1972.

Patient Dosimetry

The radiation is delivered by a Cobalt-60 teletherapy unit under the following exposure conditions. The beam is directed horizontally at a wall 342 cm away with the midline of the patient at 286 cm from the source. For whole-body exposures, the radiation beam size for the 60 percent isodose curve at the patient midline distance is a square approximately 120 cm x 120 cm. The patient is placed in the sitting position with legs raised and head tilted slightly forward. Radiation is given by delivering half the specified exposure laterally through one side of the patient; the patient is then turned and the other half exposure delivered laterally through the other side. The combined dose of the two radiation fields provides a good homogeneous dose distribution through the patient. The maximum variation in lateral dose distribution was ± 13 percent for one patient who had a lateral trunk dimension of 36 cm.

The exposure to the patient is determined using a percentage depth dose table corrected for the source-to-skin distance used for the patient. Using the corrected depth dose at patient midline ($1/2$ -lateral dimension at the trunk in the plane of the xiphoid) and a conversion factor of 0.957 rads/roentgen for Cobalt-60 gamma radiation, the midline air exposure required to give a desired midline

absorbed dose in rads is calculated. The validity of this procedure was established with measurements in an Alderson Rando Phantom using thermoluminescence dosimeters. Over the course of the study, the air exposure rates at the distance indicated above varied from 3R to 6R per minute.

For individuals receiving partial-body radiation, the teletherapy collimator is used to restrict the beam. The xiphoid is used as the boundary of the field for upper- and lower-body exposures. The lateral dimensions of the patient in the plane of the xiphoid are again used for calculating the desired midline dose. As for the whole-body exposure, the dose is delivered bilaterally. Additional information on the dosimetry aspects of this study has been published by Kereiakes *et al* (reference 27).

Analysis of Survival Data

In considering the survival data there was a lack of consistent selection bias both in recommendation that a patient be eligible for treatment and in regard to the dose. The principal investigator had no part in determination of therapy in any given case except for outlining the general principles of the therapeutic regime. The choice in the case of each patient was made by several radiation therapists, three having been associated with the project during the 10-year period. In addition, two internists have had active roles in the selection and medical care of each patient. The dose of radiation to be given was decided upon by the radiation therapist in consultation with the internist.

There are three categories of patients (those with carcinoma of the colon, lung, and breast) which are large enough to permit some analyses of survival. Each group will be discussed separately.

Survival data are given in days from the diagnosis of far advanced disease since this convention has been used frequently in the literature and permits comparison of our survival data with published reports.

Cancer of the Colon and Rectum

Twenty-nine patients with this tumor comprised the largest single category (table 1.1). In all cases the patients were classed as far advanced and in a few instances as terminal. Four patients were not included in the study for medical reasons or because the patients themselves declined participation in the study.

Table 1.1. --Cancer of colon--all cases by length of survival
of advanced disease (29 patients)

Study No. *	Age	Sex/Race	Survival After D _x (days)	Survival After R _x (days)	Dose** (rads)
106	58	F / W	40	25	300 LB
109	56	M / W	116	80	300 LB
052	60	M / W	120	91	200 LB
033	64	M / N	126	86	100
082	49	F / N	136	33	300 LB
015	61	M / N	143	32	100
007	62	M / N	181	121	100
067	52	F / N	192	163	100 LB
049	75	M / N	213	169	200 LB
050	80	M / N	220	197	200 UB
036	64	M / N	261	238	100
064	54	F / N	262	188	300 LB
091	62	F / W	295	52	200
063	38	M / W	299	244	300 LB
066	63	M / N	327	203	200 LB
107	58	F / W	347	89	200
047	57	M / W	411	147	150 LB
111	52	F / N	434	307	200
062	60	M / N	451	270	150
096	42	M / N	583	439	100
113	72	F / N	632	381	100
098/103	45	F / N	912	474	200 + 300 LB
020	69	F / N	946	885	200
006	67	M / W	982	740	54
101	76	M / N	983	864	257 LB
100	76	M / N	1,258	900	300 LB
023	44	M / N	1,261	651	200
095/104	66	F / N	1,437	704	200 + 300 LB
108	66	F / W	1,691	584	300 UB

*Study no. refers to the roster of patients described serially in Technical Reports:
Nos. 6-15⁴⁰, 18-29⁴¹, 31-36⁴², 6-64⁴³, 66-70⁴⁴, 77-82⁴⁵, 83-91⁴⁶, 92-103⁴⁷, 104-
111⁴⁸, 112-113^{personal communication; ELS}. (Super numbers 40 through 48 refer to
references at the end of this report.)

**Dose in rads at the midline. Where no letter follows the dose, whole-body radiation
was given. LB is lower-body radiation; UB is upper-body radiation. The dividing
point is the xiphoid.

Median Survival--327 days

In order to make an appropriate comparison, several published series were reviewed. Series of cases of colon cancer metastatic to liver were utilized, since they were the best found by us with appropriate time periods of metastasis available for comparison. Stearns and Binkley (reference 51), in 32 patients with colon cancer with liver metastases, found a median survival time of 11 months after palliative resection of the primary tumor; in 28 of their patients in whom only biopsy or diversion was performed, the median survival was 8 months. In 353 patients with untreated colon cancer metastatic to liver, Pestana *et al.* (reference 37) reported a median survival of 9 months. Figure 1.1 presents an analysis of 177 patients with liver metastases and no subsequent therapy reported by Jaffe *et al.* (reference 20). There is also a group of 61 patients reported by Rapoport *et al.* treated with 5 fluorouracil (reference 38). The 22 patients in our series with proven metastatic carcinoma of the colon to the liver treated by radiation are also shown in figure 1.1.

The median survival time for untreated patients was 146 days; for patients treated only with 5 fluorouracil, 255 days; and, among our patients with liver metastases, 391 days (table 1.2). A life-table analysis was performed and indicates that the treatment given to our patients was approximately equivalent to the group given 5 fluorouracil. There was no evidence that the median survival time was shortened by total- or partial-body radiation (figure 1.1). It should be appreciated that five of our patients had received or are receiving 5 fluorouracil in addition to the radiation therapy (three of these with liver metastases).

The median survival for the entire group of 29 patients (22 with liver metastases) was 327 days.

Cancer of the Bronchus

This group of 15 patients (table 1.3) had far advanced disease with distant metastases at the time of treatment. The best comparison group was from our own institution reported by Horwitz *et al.* (reference 16). The median survival of the 15 patients receiving whole-body radiation was 193 days from the time of diagnosis. The median survival of 61 patients seen at Cincinnati General Hospital from December 1961 to June 1964 was 135 days. In 15 of the 17 cases with distant metastases excluded by Horwitz *et al.* from their study (see caption to figure 1.2), the median survival was 32 days.

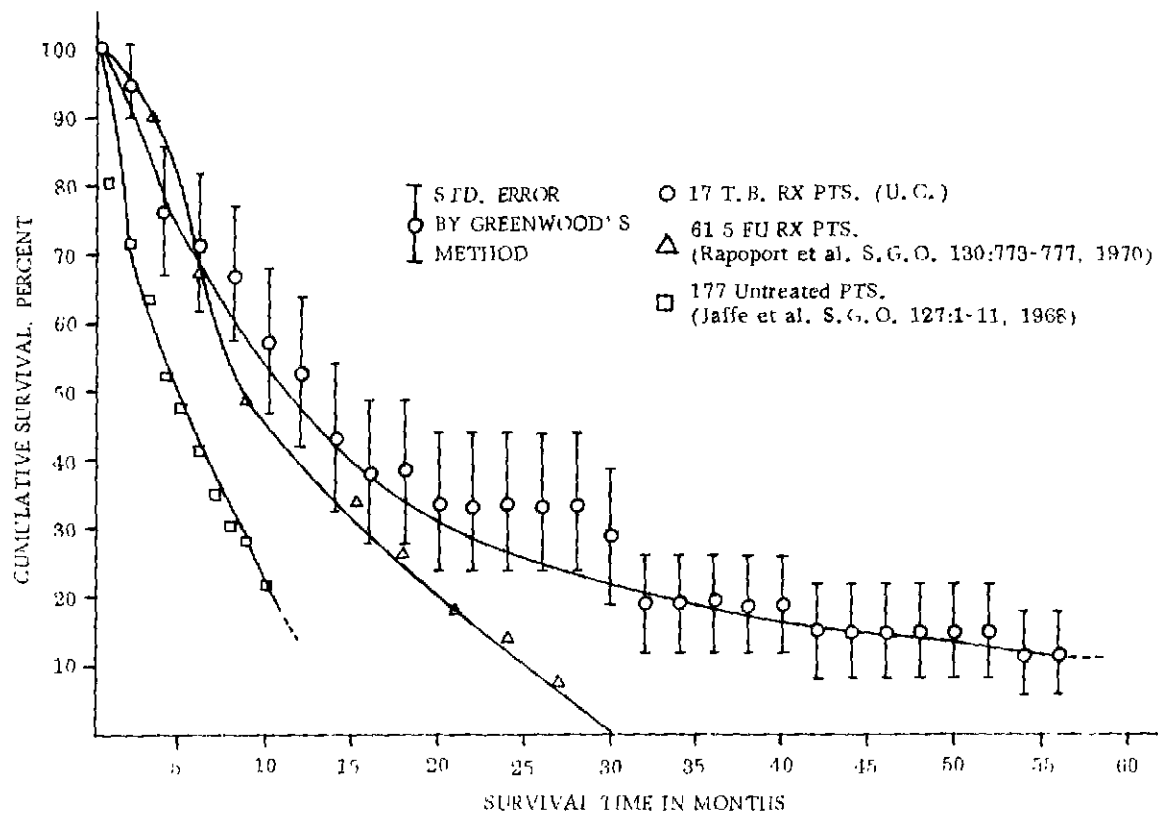


Figure 1.1. --Survival comparisons: cancer of colon metastatic to liver.

Table 1.2. --Cancer of colon--cases with metastases to liver (22 patients)

Study No. *	Survival After D _x (days)	Survival After R _x (days)
106	40	25
109	116	80
052	120	91
033	126	86
082	136	33
015	143	121
067	192	163
036	261	238
091	295	52
066	327	203
107	347	89
111	434	307
062	451	270
096	583	439
113	632	381
098	912	474
006	982	740
101	983	864
100	1,258	900
023	1,261	651
095	1,437	704
108	1,691	584

Median Survival--391 days

*See footnote to table 1.1

Table 1.3.--Lung cancer--survival in days after D_x
(15 patients)

Study No. *	Survival in Days after D _x	Survival in Days after R _x	Dose (rads)
053	57	28	200
056	103	38	100 UB
086	116	20	100
078	126	61	200
088	135	7	150
081	144	24	100
051	163	74	150
070	193	68	150
102	266	22	200 Trunk
018	333	298	200
044	349	196	100
011	419	323	100
112	683	403	100
025	797	33	150
084/097	855	643	300 UB + 100

Median Survival--193 days

*See footnote to table 1.1

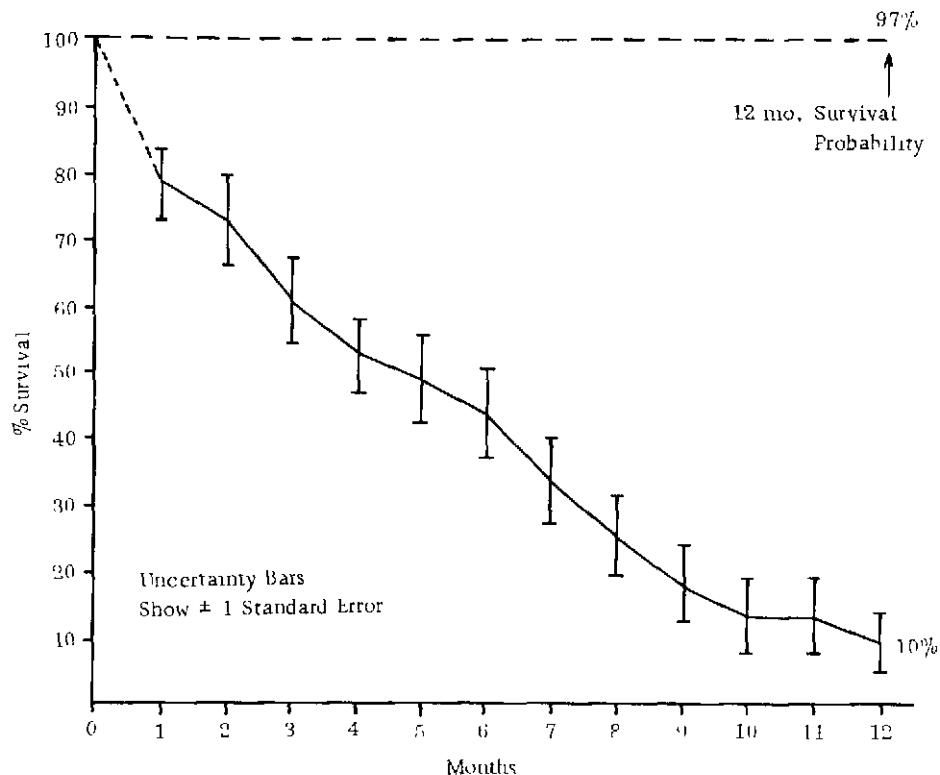


Figure 1.2. --Survival by actuarial method for 61 patients without evidence of distant metastases at first presentation.

The survival by actuarial analysis is shown for a total of 61 patients present between December 1961 and June 1964 at Cincinnati General Hospital. The only patients excluded from this group are those in whom distant metastases were present at the time of diagnosis (17 patients). If they were to be included, the 1 year survival figure would drop to about 7 percent. It is emphasized that these figures take account of all cases seen (including those apparently "early" and amenable to complete surgical resection). Although other reported figures may be somewhat higher, differences are more realistically attributable to biologic factors rather than to therapy.

From Horwitz *et al* Am. J. Roent., Rad. Ther., Nuc. Med., 1965, 93: 615-638.

This last group of patients with distant metastases constitutes the most appropriate comparison group. When the median survival of 15* patients mentioned by Horwitz *et al.* is compared with the 15 patients treated by whole-body radiation, the survival times are significantly different (Chi square 11.63, $p < 0.005$). (See figure 1.3).

Ewing's Tumor

This subgroup of three patients constituted the only one in which an attempt at curative therapy was made; all three patients are surviving. The times of survival are 854, 1,243, and 1,553 days from the time of diagnosis to 31 August 1972. The patient with the longest survival has recently developed a solitary pulmonary metastasis. The use of whole-body radiation to eliminate small clumps of cells in the disease has been reported by others (references 21 and 33).

A fourth patient with Ewing's tumor had pulmonary metastases when first seen. Therapy in that case was only palliative.

Cancer of the Breast

In 15 cases treated by us the median survival from diagnosis to death was 479 days and after treatment to death was 446 days (table 1.4). Two comparable reports in the literature include the one by the Committee on Estrogens and Androgens (reference 52) and the other by Samp and Ansfield using 5 fluorouracil (reference 49). Again a life-table analysis was done for our 15 patients and indicates that the survival of our patients appears somewhat better than that of the patients treated solely by estrogens and androgens but not quite as good as the group treated with 5 fluorouracil (figure 1.4). The patients survive longer than those receiving the "standard therapy" as described by Samp and Ansfield; this includes appropriate administration of estrogen and androgen, oophorectomy, local radiation, adrenalectomy, and hypophysectomy.

*Two of the 17 patients excluded in the Horwitz *et al.* study were treated by whole-body radiation.

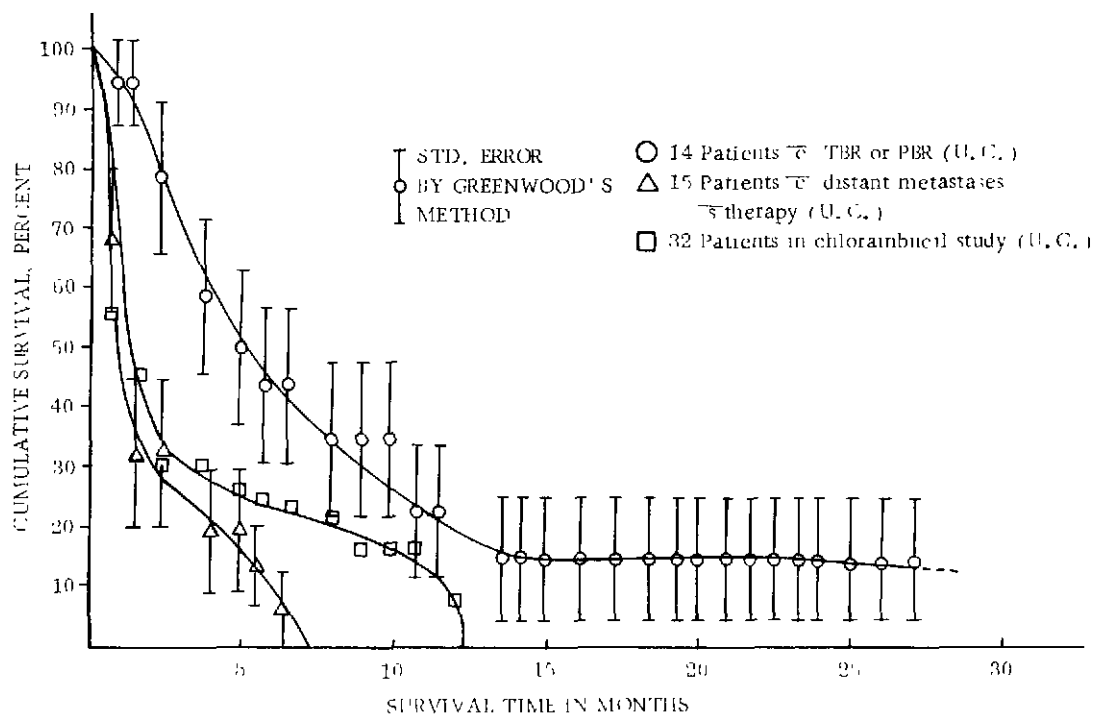


Figure 1.3.--Survival comparisons: cancer of bronchus with metastases.

Table 1.4. --Cancer of breast--survival post D_x
(15 patients)

Study No. *	Survival Post D _x (days)	Survival Post R _x (days)	Dose (rads)
089	101	16	200 Trunk
055	175	156	200 UB
029	285	152	150
060	316	30	150
045	138	25	150
022	473	10	150
094	473	354	150 Trunk
031	479	446	100
079	554	209	100
010	783	48	100
008	1056	91	100
035	1068	859	150
040	1095	1063	100
083	1098	264	100
092	1308	1143	150 Trunk

Median Survival--479 days

*See footnote to table 1.1

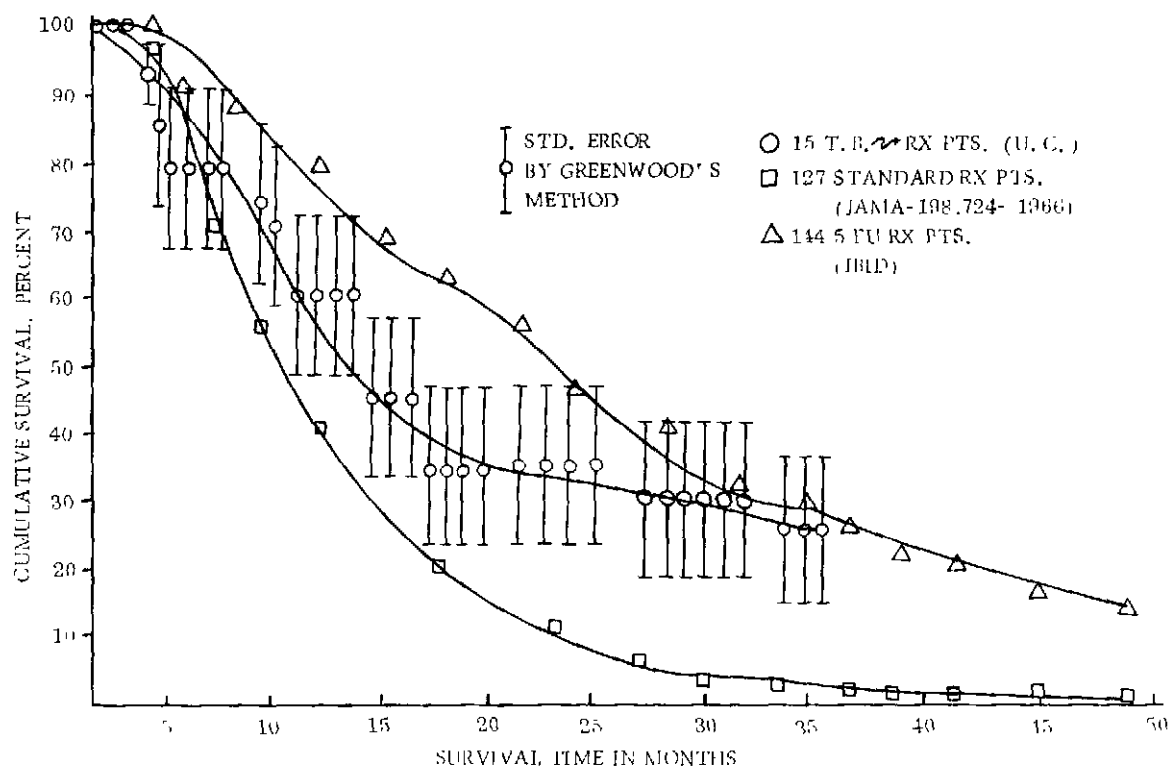


Figure 1.4. --Survival comparisons: cancer of breast with metastases.

Other Cancers

A remaining group of 25 cases reflected several different kinds of cancer. It is not possible to make an analysis of these at this point since the individual case groups are too small to warrant this.

DISCUSSION

Relation of Radiation Therapy to Patient Death

Some analyses can be made which give information on this point. The doses of whole-body radiation given could initiate only the hematological form of the acute radiation syndrome. In the healthy individual, after prodromal symptoms of malaise and vomiting lasting about 6 to 48 hours, there is a latent period lasting until 18 to 21 days after exposure. At this time there is a marked rapid fall in white cells and platelets and a less rapid fall of red cells reaching a nadir at 30 to 40 days and then recovering. These changes are associated frequently with episodes of infection and bleeding. Epilation will occur at doses over 300 rads.

Many of these patients had received much radiation and chemotherapy prior to total- or partial-body treatment, and in many cases this treatment was followed immediately by planned local therapy to various portions of the body.

If one assumes that all severe drops in blood count and all instances of hypo-cellular or acellular marrow at death were due only to radiation and not influenced by the type or extent of cancer and effects of previous therapy, then one can identify eight cases in which there is a possibility of the therapy contributing to mortality. Of this subgroup, two patients received localized radiation between total-body radiation and death at 31 and 32 days, respectively. Two had extensive previous chemotherapy and one also had local radiotherapy. In two other cases, autologous marrow transfusion was unsuccessful because the preradiation marrow was hypo-cellular. Both of these latter patients had had intensive localized radiation, and one had received intensive chemotherapy.

Of the 19 patients who died within 20 to 60 days, 11 showed clear evidence of well-functioning marrow with steady or rising white blood counts and absence of bleeding and infection at the time of death.

The time from diagnosis to death of the 24 patients entered in the study who were not treated has been analyzed. There were four who died in a 20 to 60 day interval:

	<u>No. of Deaths in 20 to 60 days</u>	<u>Patients surviving or dying at other times</u>	<u>Total</u>
Patients Not Given Radiation	4	20	24
Patients Given Radiation	19	63	82

Fisher's exact probability test yields a p value of 0.16, indicating that there is no difference between the two groups. Therefore, one may conclude that in other patients described, the effect of whole- and partial-body radiation therapy was less important in contributing to death than was the extent of disease in these patients. Another interpretation would be that a physician selecting far advanced cancer patients for a given treatment would have about the same degree of difficulty in selecting any form of treatment for these very ill patients. The same probabilities, $p = 0.19$, 0.2 , and 0.21 , are found for patients dying between 0 and 20 days post treatment, from 0 to 60 days, and from 20 to 40 days, when compared to the untreated group. Current status of survival for these 88 treated patients is as follows:

Prophylactic Therapy (Ewing's Tumor)	3
Others Surviving as of 31 August 1972	7
Deaths Possibly Attributable to Radiation	8
Deaths Attributable to Tumor	<u>70</u>
	88

Reactions From Treatment and Effects of Palliation

The acute radiation syndrome is divided into three stages. In stage 1, prodromal, nausea, and vomiting of a transient nature occur. These complaints are often highly subjective; therefore, they are not discussed with the patient before treatment. The analysis of our 88 treated patients shows that 44 percent

experienced no symptoms at all, that 27 percent had transient nausea and vomiting within 3 hours, 14 percent within 6 hours, and 3 percent within 12 hours. In only four patients (4 percent) were the nausea and vomiting of a severe nature (table 1.5). These symptoms are no greater than found after surgery or after treatment with cancer chemotherapy drugs, the reactions of which are often far more severe than those from these kinds of radiation therapy. Lahiri *et al* (reference 29) observed that when 5 fluorouracil (5 FU) is given orally at a dose of 15 mg/kg daily for 6 days, and then weekly at the same dose, nausea, vomiting, diarrhea, or stomatitis are found in 55 percent of the patients treated, and marrow depression is observed in 50 percent. A recent study by the Western Cooperative Cancer Chemotherapy Group, employing 5 FU without a loading dose at 15 mg/kg/wk for a month, reported mild to major gastrointestinal or hematologic toxicity in 85.5 percent of 430 patients (reference 17). Higgins *et al* (reference 12) in treating cancer of the colon using 12 mg/kg of 5 FU intravenously for 5 successive days observed that 27.9 percent of 359 patients experienced a toxic reaction. The same group reported one or more surgical complications following resection of colon carcinoma in 29.6 percent of 433 patients. Parsons *et al* (reference 35) note that 61 to 72 percent of patients suffering from so called radiation sickness responded favorably to placebo medication indicating that suggestibility may have a big part to play in the appearance and control of these symptoms. Mukherji *et al* (reference 34) in evaluating the effectiveness of a combination of four drugs in the treatment of 23 patients with lymphosarcoma and reticulum cell found severe myelosuppression in four patients (17 percent) and possibly attributed this depression to their deaths from infection.

During the latent period of 18 to 21 days the patient is asymptomatic. The period of manifest illness then begins with evidence of malaise, infection, and bleeding. These findings occur only with whole-body radiation and not with partial-body treatment. Also when marrow is successfully replaced these findings do not occur.

In regard to palliation, a review of patient records shows that some palliation was achieved in 56 percent and that 31 percent were made neither better nor worse (see table 1.6). In another three cases we were unable to obtain

Table 1.5. --Incidence of nausea and vomiting in 88 cancer patients receiving whole- and/or partial-body radiation therapy

	<u>Patients</u>	<u>Percent</u>
No Nausea nor Vomiting	39	44
Nausea and/or Vomiting up to 3 Hours After R _x	23	27
Nausea and/or Vomiting up to 6 Hours After R _x	12	14
Nausea and/or Vomiting up to 12 Hours After R _x	3	3
Nausea and/or Vomiting up to 24 Hours After R _x	7	8
Nausea and/or Vomiting up to 48 Hours After R _x	0	--
Nausea and/or Vomiting 48 Hours +	4	4
	<hr/> 88	<hr/> 100

Table 1. 6. --Palliative effects* of treatment in 85 patients**

	<u>Percent</u>
Relief of Pain	31
Decrease in Tumor Size	31
Increase in Activity	13
Increase in Well Being (weight gain, appetite improvement, subjective statement by patient)	30
One or More of the Above	56
<hr/>	
No Change	31
Lost to Follow-up for Evaluation of Palliation	4
Death Between 20 and 60 Days Possibly Attributable to Radiation	9

*In some of the patients there was more than one indication of improvement.
Thus, the percentages exceed 100 percent.

**Three children with Ewing's tumor received prophylactic treatment and are
not included in this analysis.

follow-up history concerning palliative effects. The three cases of Ewing's tumor are not included in this table as therapy was prophylactic.

Possible Unique Mechanisms of Whole- and Partial-Body Radiotherapy

Whole-body radiation in the doses reported herein could be effective against cancer in several ways: (1) Alteration of the immune mechanism of the body altering the balance in favor of the host; (2) By a direct effect on the metabolism of the cancer cells. In this case wide-field radiotherapy would have one advantage over drug therapy since it would reach all cancer cells without depending upon blood supply or chemical and pharmacological distribution.

Partial-body radiation could be compared to regional isolation perfusion with anti-neoplastic drugs, again being certain to reach all tumor cells within the irradiated volume and lacking the more hazardous systemic effects of total-body radiation.

The effectiveness of both methods may be explained by the fact that small tumor foci are more sensitive to treatment than large foci and that single cancer cells are more susceptible than clumps of cells.

PSYCHOLOGICAL AND PSYCHIATRIC EVALUATION OF PATIENTS

A unique and important aspect of the research work in this project has been the attempt to evaluate and distinguish between the manifestations of cancer and the effects of radiation therapy in regard to psychological and psychiatric changes. For example, others have reported on personality types in certain cancers (reference 2) but no studies were presented investigating the effects of treatment.

In 1969, we reported on the effect of total- and partial-body radiation on the cognitive and emotional processes of 16 patients (reference 11). This number has been increased to 43. These studies consisted of administration of a battery of tests to each patient in the pre-treatment phase, during sham and actual treatment, and during a 6-week post-treatment period. Tests which have been utilized included the Halstead Battery, Wechsler Bellevue Adult Intelligence Scale, some tests of intellectual impairment modified from Reitan, and the 5-minute verbal content test of Gottschalk and Gleser. There has been some change in the several tests which we have been using during this phase of the total project; i. e. not all tests have been used continually.

In the baseline data of 39 patients tested, the median intelligence quotient was 87 and the mean also 87. There were 41 percent of subjects with IQ values of 95 to 116, 47 percent between 71 to 94, and 12 percent between 63 to 70. The distribution of intelligence factors as measured by several tests is representative of the population served by the Cincinnati General Hospital.

It is clear that the intensive study and above testing has had a helpful effect in increasing the level of motivation to cooperate, as exhibited by all patients so studied.

The need for careful handling of the cancer patient by all members of the medical team is emphasized by the consistent evidence of depression over the 7-week study period. The depression is lessened with clinical improvement and attention to patient needs. It is also less in patients with long survival (over 100 days) as would be expected. Similarly, hope is directly related to survival. Anxiety dips sharply during sham treatment; it increases just prior to actual treatment, then decreases and levels off. Outward hostility tends to increase at the time of post-sham treatment, then dips and remains quite stable. Hope as measured by the content analysis of verbal behavior is related to satisfactory human relations in the patient's life situation.

USE OF AUTOLOGOUS BONE MARROW TRANSPLANTATION

Because of radiation-induced hematologic depression, autologous bone marrow storage and reinfusion were instituted in 1964. Employing the method of Kurnick (reference 28) marrow was removed from the posterior iliac crest under local anesthesia, to an average value approximating 300 cc. It was mixed with Osgood-glycerol medium and stored at -83° centigrade following a programmed temperature reduction of 1° centigrade per minute. Prior to reinfusion dextrose was added, and then the marrow was given intravenously, initially without filtration, at a rate of 50 to 60 cc per minute. The first two patients who received a marrow transfusion in our study, numbers 051 and 053, were infused with frozen marrow 24 and 19 days post-irradiation, respectively, at a time when the marrow sinusoids were relatively empty of precursor cells, with the expectation that there

would be more room for the transplant to take. Marrow viability in these two procedures was 55 percent and 57 percent (reference 45).

Patient number 051 experienced moderate hemoglobinuria not seen in patient 053 after infusion. Marrow was given in both cases 2 to 3 weeks post-irradiation; hence it was impossible to distinguish spontaneous marrow recovery from successful marrow autotransfusion.

Because hemoglobinuria had been noted, a triple filter system was developed and marrow autotransplantations on patients 070, 077, 078, 087, 090, 091, 095, 098, 099, 107, and 111 have all been performed employing this filter system (reference 48).

In marrow transplants of patients 070, 077, and 078, the delay between the removal of marrow and transfusion was 11, 2, and 0 days, respectively. The platelet count of patient 078 never fell below 125,000 per cubic millimeter, but the white blood count dropped as low as 900, suggesting possible effectiveness of the technique for the first time.

For the next eight patients the technique was, therefore, modified so that a larger volume of marrow (500 cc) was removed from the patient under general anesthesia. The patient was then irradiated and the marrow replaced intravenously on the same day as it was removed. The results in table 1.7 indicate the success attendant on the modification of this procedure. Five patients receiving 200 rads of whole-body radiation showed mean white counts to be $2,820 \pm 804$ cells per cu mm at the nadir. In seven patients given the same dose but no autograft, the level at the nadir was 850 ± 380 cells per cu mm, the two means being significantly different (table 1.8). The first patient transplanted with our new technique (patient 087) was followed in the Clinical Research Center, Cincinnati Children's Hospital, for over 6 weeks without any evidence of illness. Subsequently patients receiving these whole-body doses have only been hospitalized for a total of 5 days or less. The degree of marrow depression in the successfully transplanted patient is such that hemorrhage and infection are not observed.

The three failures in the revised transplantation technique have been patients 090, 099, and 107. Patient 090 suffered a cerebrovascular accident unrelated to her tumor or her radiotherapy. The latter two patients (099 and 107) had had

Study No.*	Type Transplant	Whole-Body Dose (rads)	Date Marrow Removed	Date of R _x	Date Marrow Reinfused	No. Cells Reinfused	Viability	Marrow Frozen	Complications of Infusion	Outcome of Autograft
051	Auto	150	4/26/65	5/1/65	5/25/65	1.6×10^9	55%	Yes	**Hemoglobin-uria for 1 Day	Did Not Take
053	Auto	200	5/4/65	5/8/65	5/27/65	1.4×10^9	57%	Yes	**None	Did Not Take
070	Auto	150	5/4/65	3/2/67	3/13/67	0.33×10^9	68%	Yes	None	Did Not Take
077	Auto	200	10/31/67	11/7/67	11/9/67	0.79×10^9	48%	Yes	Hemoglobin-uria for 12 Hours	Did Not Take
078	Auto	200	11/4/67	12/5/67	12/5/67	4.16×10^9	96%	No	None	Possible Partial Take With Platelets Never Below $125,000/\text{mm}^3$ but wbc $900/\text{mm}^3$
087	Iso	200	3/3/69	2/27/69	3/3/69	4.38×10^9	99%	No	None	Take
090	Auto	150	2/2/69	2/2/69	2/2/69	15.6×10^9	96%	No	None	Cerebrovascular Accident Killed Patient 6th Day After R _x
091	Auto	200	7/2/69	7/2/69	7/2/69	4.6×10^9	98%	No	None	Take
095	Auto	200	11/5/69	11/5/69	11/5/69	3.07×10^9	97%	No	None	Take
098	Auto	200	1/27/70	1/27/70	1/27/70	7.42×10^9	98%	No	Transient Hypotension Before Infusion	Take
099	Auto	230	3/3/70	3/3/70	3/3/70	5.32×10^9	95%	No	None	No Take
107	Auto	200	12/15/70	12/15/70	12/15/70	3.2×10^9	95%	No	None	Take Doubtful-leukopenia but no Sepsis
111	Auto	200	5/19/71	5/19/71	5/19/71	7.4×10^8	96%	No	None	Take

* See Footnote to table 1.1

** Unfiltered marrow infused

Table 1.7. --Whole-body radiation with marrow transplantation.

Table 1.8. --Results of successful iso- and auto-transplants of marrow after 200 rads midline whole-body radiation

<u>Study No.</u>	<u>Day of Leukocyte Nadir</u>	<u>Leukocyte Count at Nadir (Cells/cu.mm.)</u>	<u>Nucleated Cell Count Infused Per Kilogram Body Weight **</u>
087	26	2100	1.6×10^8
091	25	4100	2.3×10^8
095	33	2700	0.6×10^8
098	28	2200	1.7×10^8
111	31	3000	1.4×10^8
Mean	28.6	$2820 \pm 804+$	1.5×10^8
Mean of Controls*	24	$850 \pm 380+$	--

*Seven patients receiving 200 rads whole-body radiation without transplantation of marrow.

+The means differ significantly by the t test at $p < 0.001$ and by the Wilcoxon two sample test at $p < 0.02$.

**It has been estimated that 1.1×10^7 cells/kg. are required for a successful marrow iso- or autotransplant (reference 48).

widespread radiotherapy which had affected the reticuloendothelial framework necessary for stem cell development, and preliminary cell aspirates in allegedly unirradiated areas did appear hypo-cellular. Patient 107 appeared to possess normal granulocyte reserves, one of our marrow screening parameters, only because we were given an incorrectly high body weight on which to base our etiocholanolone dosage, thus falsely elevating the marrow granulocyte reserves. From this unfortunate experience we now insist that a candidate for marrow autotransplantation have a normal iliac marrow aspirate histologically, a normal bone marrow scan employing technetium-99m sulfur colloid, and normal granulocyte reserves measured with etiocholanolone (after we weigh the patient) as indicators of normal marrow function. At autopsy, patient 099, who died on day 31 post-radiation, had widespread carcinoma of the pancreas. Patient 107 survived her pancytopenia without any evidence of sepsis. Patient 111 had no significant cytopenia and her hospitalization (including autotransplant) lasted only 4 days.

This technique has been of advantage in simplifying the patient's course and eliminating the long period of hospitalization needed prior to transfusion. The possibility of reinfusing tumor cells in the untreated marrow exists, but the elimination of this problem awaits the development of successful methods of marrow allotransplantation.

SUMMARY

1. Whole- and/or partial-body radiation therapy given in single doses has shown beneficial effects in the control of certain advanced cancers. The palliative effects compare favorably with results using anti-cancer drugs as commonly reported in the medical literature.

Radiation certainly seems to improve survival in the untreated patient with cancers of colon, lung, and breast.

2. The use of autologous marrow reinfusion immediately after radiation therapy minimizes the characteristic marrow depression otherwise observed. The degree of illness following infusion is greatly lessened and hospitalization greatly shortened.

SECTION 2

THERMOGRAPHY AS A RADIOBIOLOGICAL DOSIMETER

Biological indicators of radiation injury may not always have the same degree of precision as that available from physical dosimeters (reference 54). However, the former may often be available with greater rapidity to the clinician who requires estimates of the absorbed dose to establish the degree and extent of radiation injury and hence his patients prognosis.

The effect of radiation on the skin was historically the first biological indicator employed (reference 55) and the skin erythema dose, or S.E.D., became the unit of measurement of absorbed radiation dose (reference 56). This dose effect is dependent on the area irradiated, the energy, quality, dose rate, and depth dose of the radiation employed (reference 57).

Infrared thermography has been employed with some success in the diagnosis of numerous medical conditions (references 58 through 62). Biophysical aspects of this technique have been reviewed elsewhere (reference 63).

The purpose of this study has been to determine if thermography, a technique with sensitivity to temperatures changes of fractions of a degree, could detect early skin-temperature changes in patients receiving radiotherapy.

Materials and Methods

Six patients receiving Cobalt-60 radiotherapy for a variety of malignant neoplasms were scanned serially with an infrared sensitive thermograph during the course of treatment. Informed consent was obtained from each individual. These individuals were instructed to take no medication for 24 hours prior to the study. None had smoked a cigarette or ingested hot or cold beverages for 2 hours prior to thermography. Clothing was removed from the area of the body to be studied in a closed room with temperature maintained at $73 \pm 1^{\circ}\text{F}$. A 20-minute-period was allowed for thermal equilibrium (reference 63). The patient lay supine or prone on a table during the study, and the infrared radiation emitted by his body was reflected into a Barnes/Bofors Model M-101 Medical Thermograph by a front-silvered mirror angled above him. The radiation was converted

to an electrical signal used to produce visible light photographed by a Polaroid camera.

Symmetric areas on each patient's body, 1-inch square, were measured from the midline to correspond exactly to the irradiated region and were marked with indelible ink. Thermograms were first obtained from the skin 20 minutes after the marking process, and then slender pieces of aluminum foil were overlaid on the ink mark delineating each area. The margins of these symmetrical regions appeared as dark lines on this second thermogram because of the low emissivity of the shiny surface. The outlined areas on the second thermogram were initially transferred to the first picture by superimposing the Polaroid films and punching pin holes along the border of the outlined area. It was subsequently determined during these experiments that the thin boundaries of foil did not change the temperature of the enclosed skin.

A precalibrated thermal-gray scale, containing squares of known constant temperature from 29°C. through 38°C. was positioned to appear on each scan. The temperature of each square was unchanged on recalibration by the manufacturer, confirming the validity of using this scale for measuring heat emission.

Densitometer readings were obtained from the thermal-gray scale and plotted against the temperature reading of this scale. The resultant curve was used to obtain the skin temperatures of the two sides of the body being compared from the densitometer readings of the 1-inch square areas seen in the thermograph. Two densitometers were employed*+ but gave identical readings for each picture. A new temperature-densitometry curve was plotted for each thermogram examined. Maximum error attributable to the densitometer, obtained from multiple readings of the same areas of selected thermograms was 0.133°C. (mean \pm 2 S. D.). The thermography equipment which we employed had no intra-thermogram drift according to the manufacturer, and the inter-thermogram drift was said to be linear.

*Barnes Engineering Co., 30 Commerce Rd., Stanford, Connecticut 06902.

+Quantalog Model TD 100, Macbeth Instrument Corp., P. O. Box 950, Newburgh, N. Y.

Since patients were followed throughout their radiotherapy, the variables of number of fractions and total time relative to total dose made any simple summation of accumulated dose difficult to evaluate. The concept of nominal standard dose (N.S.D.) was, therefore, employed to correlate the biologic effect of radiation dose with skin temperature (reference 11). The N.S.D. is employed as the best available estimate of the equivalent single dose. Ellis finds the total dose, $D = (\text{N.S.D.}) (T^{0.11}) (N^{0.24})$ where D and (N.S.D.) are in rads, T is in days, and N is the number of the fractions.

From 13 healthy volunteers (five women and eight men, ages 17 to 48) each of whom had multiple thermographs taken on separate days, we established the normal upper limits (mean \pm 2 S.D.) of the difference between symmetric areas of the trunk. The data in table 2.1 correspond well with the approximations of others (references 63, 65, and 66). Variation in skin pigmentation does not affect infrared radiation from the body (reference 63). We found no differences in thermal symmetry between men and women.

Results and Discussion

Table 2.1 indicates those limits which, when exceeded, indicate a significant difference between symmetric area ($p < 0.05$) when studied with the above techniques.

The results of thermographic determinations on irradiated and the corresponding symmetric nonirradiated areas for each of our patients are listed in table 2.2 with the type of malignancy for which each was receiving Cobalt-60 radiotherapy.

Patients two and six had thermal asymmetry exceeding the upper limits for normals listed in table 2.1 prior to irradiation, but patients prior to irradiation cannot be considered normal, both because of untreated tumor and previous surgery in these areas. These factors naturally will cause deviations from the normal degree of thermal asymmetry. Nevertheless, the normal asymmetry values in table 2.1 were exceeded only two times preirradiation.

With nominal standard--or single--doses up to 1,453 rads (patient five), we were unable to detect significant differences between irradiated and nonirradiated sides with the thermograph. In none of these patients was there visible erythema or subjective discomfort in the irradiated area.

Table 2.1. --Normal maximum differences in symmetric areas of the body

Head--Neck	1.0 ⁰ (reference 63)
Anterior Chest	0.78 ⁰
Posterior Chest	1.23 ⁰
Anterior Upper Abdomen (Xiphoid to Umbilicus)	1.38 ⁰
Anterior Lower Abdomen (Umbilicus to Pubis)	1.42 ⁰
Lumbosacral Region	1.42 ⁰

Table 2.2. --Skin temperature of patients receiving Cobalt-60 radiotherapy
(degrees centigrade)

Patient 1--Testicular Seminoma

Posterior Lumbo-Sacral:

Right Rad		Left Non-Rad		ΔT		N. S. D.
*U	*L	U	L	U	L	
33.25	33.70	32.70	32.90	0.55	0.80	674.1
33.50	34.05	34.10	33.60	-0.60	0.45	961.9

*U = upper, L = lower part of irradiated area, each 1 inch square.

Correlation N. S. D. and T: L: $r = 0.41$ U: $r = 0.87$

ΔT insignificant throughout.

Patient 2--Bronchogenic Carcinoma

Chest:

Left Rad		Right Non-Rad		ΔT		N. S. D.
U	L	U	L	U	L	
34.80	33.85	33.85	33.45	0.95	0.40	0
35.15	34.45	34.70	34.35	0.45	0.10	861.5

Correlation N. S. D. and T: U: $r = 0.19$ L: $r = 0.45$

ΔT insignificant throughout.

Table 2.2. --(Continued)

Patient 3--Renal Carcinoma

Upper Abdomen:

Left Non-Rad		Right Rad		N. S. D.	ΔT	
U	L	U	L		U	L
36.25	36.30	36.10	35.65	473.1	0.15	0.65
33.65	33.65	33.15	33.45	473.1	0.50	0.20

ΔT 's not significant.

Patient 4--Bronchogenic Carcinoma

Anterior Chest:

Left Rad				Right Non-Rad				ΔT				N. S. D.	
*UL	UM	LL	LM	UL	UM	LL	LM	UL	UM	LL	LM		
34.00	34.70	34.30	35.35	33.40	34.60	34.40	34.95	.60	.10	.90	.40	961.0	
34.35	35.15	34.30	35.30	34.00	34.80	34.50	35.55	.35	.35	-.20	-.25	961.0	

*UL = upper lateral, UM = upper medial, LL = lower lateral, LM = lower median.
 ΔT 's not significant.

Table 2.2. --(Continued)

Patient 5--Malignant Melanoma

Anterior Abdomen:

Rad				Non-Rad				N.S.D.		ΔT			
*UL	UM	LL	LM	UL	UM	LL	LM			UL	UM	LL	LM
34.60	35.25	--	35.40	34.05	33.90	--	33.75	1452.6		0.55	1.35	--	1.75

*UL = upper lateral, UM = upper median, LL = lower lateral, LM = lower median areas in field.

The ΔT for the UM and LM are statistically significant.

Patient 6--Bronchogenic Carcinoma, Metastatic

Anterior Upper Abdomen:

Rad		Non-Rad		ΔT		N.S.D.
U	L	U	L	U	L	
33.20	33.65	34.24	34.00	-1.05	-0.35	0
33.20	33.30	33.25	33.00	-0.05	-0.30	945.7

Correlation between N.S.D. and T: LM: $r = 0.74$ UM $r = 0.73$

ΔT insignificant throughout radiation period ($\Delta T \leq 0.30$).

The direct heat imparted to the skin from gamma rays, even assuming total absorption, is itself negligible and may be calculated as $2.39 \times 10^{-6} \text{ }^{\circ}\text{C. per rad}$ (reference 14).

For several of our patients we obtained thermographic readings for a number of stages of their radiotherapy. For those patients we attempted to determine the correlation between radiation dose and the difference in temperature between the irradiated and nonirradiated sides (ΔT). The correlations were generally low. We obtained occasional high correlations, but they were both positive and negative. For example, patient one, with a N.S.D. of 962 rads had a correlation of -0.87 for a region within his posterior lumbo-sacral area, while patient six, with a N.S.D. of 946 rads, had a correlation of +0.73 for an area in his anterior upper abdomen. Hence, no correlation can be drawn between radiation doses and the ΔT at radiation doses up to 1,000 rads. In all cases where the correlation appeared high, the ΔT did not exceed the upper limit for normal thermal asymmetry.

In the only case with a N.S.D. exceeding 1,000 rads of ^{60}Co irradiation to the trunk, an abnormal ΔT occurred: patient five, with N.S.D. of 1,453 rads, receiving radiation to the abdomen.

During the brief period of availability of the thermograph only one patient was receiving 250 kVp X-ray therapy. Her N.S.D. was 1,930 rads (table 2.3), but the contribution of active superficial breast cancer to the abnormally high ΔT of 1.40°C. prevents any conclusion as to dose-response relationship of this quality of radiation and skin temperature.

The threshold erythema dose for various qualities of radiation rises with the energy applied (reference 67) and is given as 960 rads for 1 meV. Our limited human data are in agreement, with no significantly abnormal ΔT at doses under 1,000 rads. The one patient whose skin temperature did rise significantly to exceed our normal values received the highest N.S.D. to his trunk, 1,453 rads.

Thus, sophisticated thermographic equipment may add little to the doses one can estimate by visible erythema. We have assumed that the nominal standard dose is the equivalent of a single dose. The N.S.D. as calculated herein correlates well with erythema doses reported elsewhere (reference 67).

Table 2.3. --Breast carcinoma 250 kVp X-ray anterior chest

Rad	Non-Rad	N. S. D.	ΔT
35.40	34.00	1930.2	1.40

This ΔT is significant.

Skin changes in man do not appear to be a good early biologic radiation dosimeter. The effects of doses to the trunk well below those we can detect with thermography will be apparent from early gastro-intestinal and hematologic changes (reference 68).

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13. ABSTRACT Section 1 of this report presents the results of whole- and partial-body radiation given to 85 adults with far advanced cancer and three children with Ewing's sarcoma between 19 February 1960 through 31 August 1971. These studies fall into Phase I (is the treatment toxic) and Phase II (is the treatment effective but with no controls). All patients gave informed consent in accordance with the Faculty Research Committee of the University of Cincinnati who has reviewed and approved the project regularly. In patients with carcinoma of the colon metastatic to liver, survival after one to two treatments was about equivalent to that achieved with 5-fluorouracil therapy. In patients with bronchogenic cancer with metastases there was significant improvement in survival cancer, survival was better than that of patients treated solely with estrogens and androgens but was not quite as good as in a group treated with 5 FU. Three children receiving prophylactic radiation for Ewing's tumor are living, although there has been a pulmonary recurrence in one child. No significant difference in time to death could be found when comparing treated and untreated patients in this series. Reactions from treatment were no more severe and in general less than those encountered with chemotherapy. The use of autologous marrow reinfusion immediately after radiation therapy minimizes the characteristic marrow depression otherwise observed. The degree of illness following infusion is greatly lessened and hospitalization greatly shortened. Section 2, an evaluation of thermography in determining skin changes and as an index of dose levels to skin, is less useful than the obvious and well documented clinical findings.		

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